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13. ABSTRACT ***(Maximum 200 Words)***

Purpose: To analyze to what extent women born extreme premature and women characterized as small for gestational age at birth differ with regards to breast cancer risk as adults.

Scope: To identify all women within a study base of 290,000 female births during the years 1925 to 1949 in central Sweden born before the 35th gestational week and/or with a birth weight below 2,000 grams. The women in the cohort still alive in 1958 have been followed up for occurrence of breast cancer through linkage with Swedish registries.

Major findings: There were 1,847 survivors January 1, 1958, of which 90 were diagnosed with breast cancer up through 1996. Preliminary analyses strongly indicate that women born extremely premature compared to those born small for gestational age have an increased risk of breast cancer.

Conclusion: Our findings strongly indicate that early hormonal exposures are of importance for the risk of breast cancer later in life.

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Introduction

In 1990, Dimitrios Trichopoulos formulated the hypothesis that intrauterine exposures could be of major importance for the lifetime risk of breast cancer (Trichopoulos 1990). This hypothesis has been tested both in Sweden (Ekbom et al 1992, Ekbom et al 1997) and in the United States (Sanderson et al 1996, Michels et al 1996) and a weak association with increasing birth weight leading to an increased risk for breast cancer has been found. Extreme prematurity has in two of these studies (Ekbom et al 1992, Ekbom et al 1997) been associated with an increased risk of breast cancer, a finding confirmed in a small cohort study which also served as a pilot study for the present project (Ekbom et al 2000). Similarly, there have been hints that small for gestational age is associated with a decreased risk for breast cancer (Ekbom et al 1992, Ekbom et al 1997). The purpose of the present study was to test this hypothesis in a large cohort study consisting of all female births during a 25-year period in central Sweden. All women born in Stockholm, Uppsala and Sundsvall before the 35th gestational week and/or with a birth weight of 2,000 grams were traced and followed up for cancer occurrence.

Body

Task 1:
Apply to, and negotiate with, the Swedish Data Inspection Board and appropriate Ethical committees for permission to do the study and to link the cohort with the Swedish Cancer Registry, the Swedish Death Registry and the Swedish Emigration Registry.
* Accomplished.

Task 2:
Employ two abstractors for the field work in the different archives.
* Accomplished.

Task 3:
Retrieve the information from the ledgers at the different delivery centers as well as start tracing women through population ledgers up to January 1st, 1947.
* Accomplished.

Task 4:
Tracing all women through the population ledgers.
* Should have been accomplished by April 2000, but was not finalized until August 2000.

Task 5:
Linkage performed with the Swedish Death Registry, Emigration Registry and Cancer Registry.
* Due to the delay for a complete tracing the data was not delivered from the Statistics Sweden and the National Board of Health until November 14, 2000.

Task 6:
Analysis completed.
* Due to the delay of task 6 we have not been able to finalize the analyses yet. They will be finalized at the end of this year.

Task 7:
Final report as a paper is completed.
* Due to the delay of task 6 this has not yet been finalized. Preparations are, however, on the way.

Preliminary results

We identified 1,857 women with a birth weight of less than 2,000 grams or a gestational age of less 35 weeks (see table below).

Gestational age	N
<33	567
33-34	718
>34	572

After linkage with the Swedish Cancer Registry we could identify 90 cases of breast cancer.

Preliminary analyses show distinct differences in cumulative incidence of cancer in those born before the 33rd gestational week as a higher occurrence compared to those born thereafter.

The preliminary data support the a priori hypothesis that extreme prematurity is associated with an increased risk for breast cancer. Thus, early hormonal exposures are further indicated to be of importance for the life time risk of breast cancer.

Key research accomplishments

- We identified a cohort of women born extreme premature or with a birth weight less than 2,000 grams in a population-based setting.
- We identified all breast cancer cases in the cohort (n=90).
- Preliminary analyses strongly indicate that extreme prematurity is associated with an excess risk of breast cancer.

Reportable outcomes

Manuscripts, abstracts, presentations
- The pilot study and the research project have been presented at the Era of Hope meeting as a poster. The abstracts are enclosed in the appendices (Appendix 1).
- The pilot study has been published as a paper in Journal of the National Cancer Institute (Appendix 2).

Conclusions

The preliminary results of this cohort study strongly indicate that early hormonal exposures are of great importance for the future risk of breast cancer. Our results indicate that women born before the 33rd gestational week is a group, which seems to be especially vulnerable for this outcome. Future research should therefore include studies on the specific characteristics among women with breast cancer and such a medical history. Such a study could provide additional important clues of the etiology of breast cancer.

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Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S. Risk of breast cancer in prematurely born women. Natl Cancer Inst 2000;92:840-841.

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Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990;335:939-40.

Appendices

Appendix 1: Abstracts Era of Hope meeting

Appendix 2: Article "Risk of breast cancer in prematurely born women" by Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S published in Natl Cancer Inst 2000;92:840-841.

List of personnel that have received salaries from the project

Anders Ekbom, PI, professor
Incan Gedin, Abstractor
Magnus Kaijser, M.D., doctorial student
Ulrika Lund, Abstractor
Anna Simlund, Abstractor

IS THE RISK FOR BREAST CANCER INCREASED IN PREMATURELY BORN WOMEN?

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Background. A causal relationship has been hypothesized between early exposures to elevated levels of estrogen and breast cancer. Assessing the risk of future breast cancer in girls born before the 33rd gestational week, who have excessive ovarian production of estradiol during the postnatal period, could be one way to test this hypothesis.

Methods. In a pilot study we identified all singleton women born before the 35th gestational week, or born later but with a birth weight below 2,000 grams, at the two major delivery centers in Stockholm between 1925 and 1934 and still alive January 1, 1958, the date when the Swedish Cancer Registry started to operate. The standardized incidence ratio—the ratio of observed cancers to expected—was used as a measure of relative risk.

Results. Among the 273 women who met the eligibility criteria, we found 12 cases of breast cancer. The standardized incidence ratio was 6.7 (95% CI 1.4-19.2) for women born before the 31st gestational week and 2.3 (95% CI 0.7-5.3) for those born in gestational week 31–32. The increased risk of developing breast cancer before the age of 50 was even more pronounced: 12.2 (95% CI 1.5-45.1) and 4.1 (95% CI 0.8-11.9), respectively.

Conclusions and work on the way. In the pilot study, extreme prematurity is associated with increased risk for breast cancer, which indicates a causal relationship between breast cancer and the specific characteristics of the postnatal endocrinology. In order to enhance the statistical power we are presently identifying an enlarged cohort consisting of 2,500 women born before the 31st gestational week between 1925 to 1949 at different delivery centers in Sweden.

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Early exposures, especially hormones, have been implicated as being of importance for the risk of breast cancer in adults. Girls born before the 33rd gestational week, will during the months following birth be exposed to extremely high hormonal levels due to an insufficient feedback system affecting the ovaries. In a pilot study we could demonstrate an up to 10-fold increased risk of breast cancer among women born before the 33rd gestational week.

We are presently identifying 2,500 women born before the 35th gestational week and/or with a birth weight less than 2,000 grams, which we will follow up for breast cancer occurrence. If the results from the pilot study can be reproduced in this enlarged cohort, that will further broaden our understanding for the etiology of breast cancer. Moreover, we would also be able to identify a subgroup of women with an especially high risk for developing breast cancer. This subgroup, due to improved perinatal care, will constitute about 1% of the female population in the birth cohorts born from 1960 and onwards.

BRIEF COMMUNICATION

Risk of Breast Cancer in Prematurely Born Women

Anders Ekbom, Gunnar Erlandsson, Chung-cheng Hsieh, Dimitrios Trichopoulos, Hans-Olov Adami, Sven Cnattingius

Epidemiologic studies of breast cancer [reviewed in *(1)*] have for several decades focused on the role of reproductive factors during adult life. A new line of research opened when it was suggested that perinatal events and conditions may influence a woman's breast cancer risk throughout her life *(2,3)*. Five separate epidemiologic studies *(4–8)* have tested this hypothesis. Besides a weak association between increasing birth weight and increased risk for breast cancer [seen in four studies *(4–7)*], most pronounced in women with premenopausal breast cancer, two studies *(4,7)* also demonstrated an inverse association between preeclampsia during pregnancy and breast cancer in the offspring out of three that examined this hypothesis. This finding supports indirectly that early hormonal exposures affect risk of breast cancer, since preeclampsia is characterized by decreased levels of pregnancy hormones *(9,10)*.

Two independent observations led to the present investigation. One study *(7)* indicated that female babies born prematurely (before the 33rd gestational week) had an increased risk for breast cancer. Girls born before the 33rd gestational week have markedly increased levels postnatally of gonadotropins *(11)* that stimulate the ovaries to produce excessive amounts of estradiol during several months after birth *(12,13)*. Since women born before the 33rd gestational week during the first half of the 20th century constitute a very small fraction, 10 of 1068 case patients, of breast cancer patients in the study mentioned above, this will not affect the results in the studies analyzing the association between birth weight and breast cancer risk. However, women born extremely preterm are an ideal group in which to test the hypothesis of an association between early exposures to elevated estrogen levels and breast cancer.

In the city of Stockholm, Sweden, there were two major delivery centers covering defined geographic areas from 1925 through 1934. There were around 60 000 deliveries uniformly documented on charts where names and addresses of the parents, gestational age calculated from the date of last menstruation, and birth weight could be retrieved. The charts have been saved in the city archive. We were able to trace the offspring by using church parish ledgers up to January 1, 1947, when all Swedish residents were assigned a national registration number, which is used as an identifier in the Swedish databases. The study was approved by the local ethical committee in Stockholm.

Extremely premature children during this time period were treated in a uniform manner. They stayed at the maternity ward for about 24 hours, and survivors were then transferred to a pediatric ward, where they were offered nutritional support. No other care or diagnostic procedures, such as x-ray examination of the lung, were provided. The children stayed at the ward for 2–3 months. The 1st year after birth, the mortality was extremely high but did not differ substantially from that expected in the rest of the population.

We examined manually and individually all 60 000 delivery charts to identify girls born before the 35th gestational week and those with a birth weight under 2000 g—regardless of gestational age. (Girls within the highest 1% of birth weight for the specific gestational week were excluded.) The study was restricted to women still alive on January 1, 1958, the starting date of the Swedish Cancer Registry.

A total of 273 women met our eligibility criteria; their distribution by gestational age is shown in Table 1. The occurrence of breast cancer was ascertained through the Swedish Cancer Registry for the period from 1958 through 1992. We calculated the expected number of breast cancer cases under the assumption that the risk was similar to that of the background population (also derived from the Swedish Cancer Registry). Person-time at risk (from January 1, 1958, until the end of follow-up, December 31, 1992) was calculated with allowance for death or emigration, both of which were ascertained through the Swedish registry. The standardized incidence ratio, i.e., the rates of observed-to-expected numbers of cancers, was used as a measure of risk. The 95% confidence interval (CI) was calculated under the assumption that the observed number of cancers followed a Poisson distribution.

In the analysis, we stratified the women into one of four groups: 1) born gestational weeks 29–30, 2) born gestational weeks 31–32, 3) born gestational weeks 33–34, or 4) born after the 34th gestational week but with a birth weight less than 2000 g. (In this last group, we also included deliveries where the girls weighed <2000 g without any information of gestational age.)

During follow-up, breast cancer was diagnosed in 12 women, seven of whom were younger than 50 years (Table 1). In women born before the 31st gestational week, the risk for breast cancer was increased 6.7 times (95% CI = 1.4–19.5), and the risk before the age of 50 years was increased 12.2 times (95% CI = 1.5–45.1). A twofold to fourfold increased risk was observed among women born in the 31st or 32nd gestational week. With longer gestational time, the relative risk of breast cancer declined. There was even some evidence that women born small (i.e., birth weight <2000 g) and after the 34th gestational week were at lower risk, in accordance with the results of previous studies *(2,4)*.

Our main finding—that women born before the 33rd gestational week run a

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See "Note" following "References."

Table 1. Incidence of breast cancer among women born in Stockholm, Sweden, 1925 through 1934, either before the 35th gestational week or later, but with birth weight less than 2000 g*

Gestational age, wk	No. of women	All ages			<50 y old		
		No. of breast cancer cases	SIR†	95% CI‡	No. of breast cancer cases	SIR†	95% CI‡
<31	13	3	6.7	1.4–19.5	2	12.2	1.5–45.1
31–32	53	5	2.3	0.7–5.3	3	4.1	0.8–11.9
33–34	105	3	0.7	0.1–2.0	2	1.3	0.2–4.7
⩾35†	102	1	0.2	0.01–1.3	0	0.0	0.0–2.7
Total	273	12			7		

*Gestational age 35 weeks or longer with birth weight less than 2000 g, indicating small for gestational age.

†SIR = standardized incidence ratio. SIR = observed divided by expected number of cases, a measure of relative risk.

‡CI = confidence interval.

substantially increased risk of breast cancer—supports the hypothesis of a relationship between the perinatal hormonal environment and the risk for breast cancer. Selection bias cannot explain the results because the study was essentially a population-based study, since the two centers at which the children were delivered in Stockholm encompass two defined areas where, as a rule, all deliveries from these areas were supposed to take place. Moreover, the study was prospective, with complete, nondifferential follow-up. Misclassification of gestational age is possible but would only attenuate the results. We did not identify any plausible confounding factor; most importantly, none of the children had undergone frequent or high-dose x-ray exposures to the chest *(14)*. Chance findings cannot be ruled out, but the results were in accordance with observations made in our previous case–control study *(7)*. Indeed, the excess breast cancer risk among the extremely prematurely born, low birth weight notwithstanding, suggests that the unusual endocrinology that characterizes extremely premature girls is the most likely explanation.

We can only speculate about the mechanism(s). An immature hypothalamic–pituitary feedback system might entail increased stimulation of the ovaries by high levels of gonadotropins leading to an excessive secretion of estradiol. Estrogens could favor the development of mutations through enhanced cell proliferation when the breast tissue is partly undifferentiated. Evidence *(15)* also indicates that high levels of estrogen have a direct mutagenic potential.

In our study base, girls born before the 33rd gestational week constituted approximately 0.2% of all survivors as of January 1, 1958. Today in Sweden, children born before the 33rd gestational week constitute about 1% of all live births. In the 1970s, 50% survived, whereas today more than 80% survive *(16)*. If our risk estimates are correct, those women will, in the next 10–20 years, constitute close to 5% of all women with a new diagnosis of breast cancer.

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Note

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